

Human schistosomiasis in the post mass drug administration era

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Profound changes are occurring in the epidemiology of schistosomiasis, a neglected tropical disease caused by a chronic infection with parasitic helminths of the genus *Schistosoma*. Schistosomiasis currently affects 240 million people worldwide, mostly in sub-Saharan Africa. The advent and proliferation of mass drug administration (MDA) programmes using the drug praziquantel is resulting in substantial increases in the number of people, mainly children aged 6–14 years, being effectively treated, approaching the point where most people in endemic areas will receive one or more treatments during their lifetimes. Praziquantel treatment not only cures infection but also frees the host from the powerful immunomodulatory action of the parasites. The treatment simultaneously enhances exposure to key parasite antigens, accelerating the development of protective acquired immunity, which would take many years to develop naturally. At a population level, these changes constitute a substantial alteration to schistosome ecology in that the parasites are more likely to be exposed not only to praziquantel directly but also to hosts with altered immune phenotypes. Here, we consider the consequences of this for schistosome biology, immunoepidemiology, and public health. We anticipate that there could be substantial effects on chronic pathology, natural immunity, vaccine development strategies, immune disorders, and drug efficacy. This makes for a complex picture that will only become apparent over decades. We recommend careful monitoring and assessment to accompany the roll-out of MDA programmes to ensure that the considerable health benefits to populations are achieved and sustained.

Introduction

One of the greatest advances in improving human health in the tropics, particularly in child health and development, has been the development of anthelmintic drugs and their subsequent distribution in mass drug administration (MDA) programmes. MDA refers to the drug treatment of targeted populations irrespective of individual infection status. MDA was first used in the 1930s in attempts to control malaria with the drug plasmoquine, with mixed results.¹ MDA campaigns for schistosomiasis were done in Egypt in the 1950s using tartar emetic,² but because tartar emetic had low efficacy and needed many daily injections, this was a false dawn for schistosome MDA. When praziquantel became available in the 1980s, MDA against schistosomiasis was slowly adopted as the major control strategy. Praziquantel is safe and efficacious, with cure rates as high as 100% as shown by parasitological methods of egg counts using urine filtration³ or stool Kato Katz technique.⁴ The drug is given as oral tablets at a dose of 40 mg/kg bodyweight in Africa⁵ in both adults and children and 50 mg/kg in adults and 60 mg/kg in children in South America.⁶

Current global initiatives following the guidelines for preventative chemotherapy set out by the WHO have implemented regular school based de-worming strategies to reduce development of severe morbidity, promote child health, and improve the developmental potential of children. Many affected countries have now created helminth and trachoma control programmes targeting multiple diseases and specific vulnerable groups within the population. These programmes are primarily focusing on onchocerciasis, lymphatic filariasis, trachoma, schistosomiasis, and soil transmitted helminths and are aimed at reducing infection and morbidity. Lymphatic filariasis and onchocerciasis programmes are both

aiming for elimination, but schistosomiasis and soil transmitted helminth programmes lag well behind. One exception is Zanzibar, where success in reducing the prevalence of schistosome infection has suggested the possibility of elimination.⁷

Global MDA programmes

In 2014, 56 million people in 27 countries (20 of them in Africa, with the other seven in Asia and South America) received praziquantel treatment for schistosomiasis and the aim is to increase this number steadily over the years 2016–20. In sub-Saharan Africa alone, it is estimated that some 100 million school-aged children (aged 6–14 years) require treatment for schistosomiasis,⁸ and Merck Soreno have pledged to donate 250 million tablets of praziquantel annually to meet the need for treatment. With additional praziquantel also available from World Vision, the World Bank, and the UK Department for International Development, sufficient amounts should be available to deliver about 130 million treatments annually. Whether countries will have the funds and capacity to deliver these drugs to the rural populations will be the factor that will decide whether schistosomiasis will be effectively controlled in the near future. Indeed, better implementation has been suggested as a potential reason for the greater effectiveness of MDA programmes in China compared with the Philippines.⁹ However, it is clear that we are fast approaching the point where, for the first time in history, most people infected with schistosomiasis will receive treatment at some point during their lives (figure 1). In any event, it will be important to investigate the consequences of this massive MDA so that the success of the control programmes and the reduction of transmission and infection can be measured, and so that we can understand any changes in

Lancet Infect Dis 2017;
17: e42–48

Published Online
December 14, 2016
[http://dx.doi.org/10.1016/S1473-3099\(16\)30475-3](http://dx.doi.org/10.1016/S1473-3099(16)30475-3)

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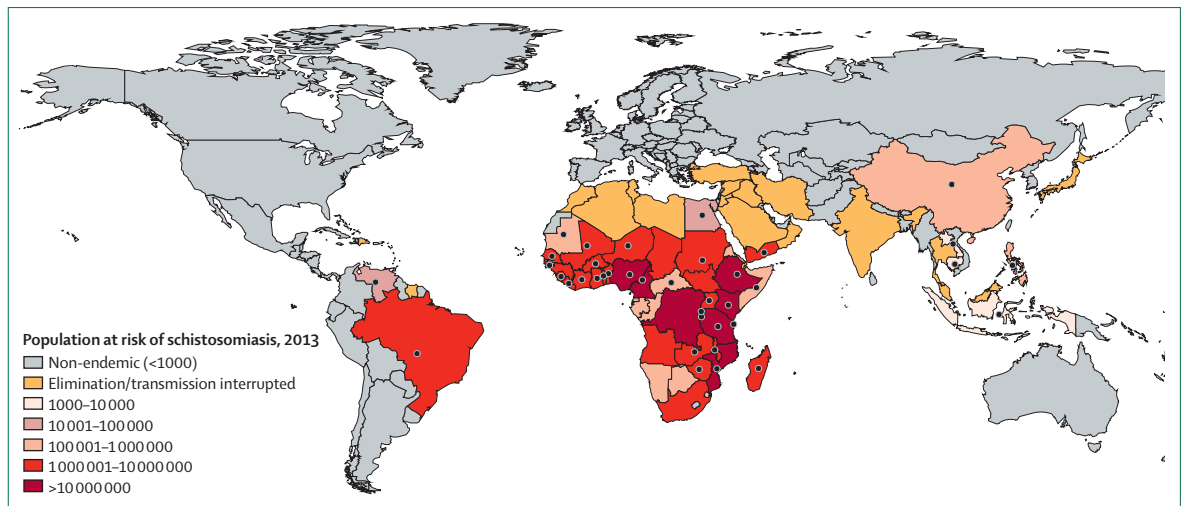


Figure 1: Map showing the estimated number of children aged 6–14 years requiring annual treatment for schistosomiasis (preventative chemotherapy) in countries where the disease is endemic

Black dots indicate countries where there has been a MDA programme using praziquantel within the past 5 years (2010–15). Data obtained from the World Health Organization Preventative Chemotherapy databank. MDA=mass drug administrations.

For the World Health Organization Preventative Chemotherapy databank see http://www.who.int/neglected_diseases/preventive_chemotherapy/sch/en/

the epidemiology of schistosomiasis resulting from unprecedented levels of drug pressure.

We have been involved in implementing, monitoring, and assessing schistosome control programmes in several countries in Africa. Concurrently, we have been undertaking basic scientific research to inform the development and delivery of helminth interventions, including schistosomiasis control strategies. Our research has led us to contemplate what the human health and parasite population landscape will look like in both the short and longer terms following widespread MDA to control schistosome infection and morbidity.

Malaria MDA programmes offer valuable lessons on how to anticipate both failure and success in population-based parasite control programmes.¹⁰ However, interpretation of the effect of malaria MDA programmes is complicated by the fact that many malaria campaigns used both MDA and integrated vector control approaches. For schistosomiasis, most people recognise that improvements in water supplies, sanitation, and hygiene (WASH), will be needed if disease is to be eliminated. Historically, some countries, notably Egypt, have included WASH, as well as mollusciciding to reduce numbers of intermediate host snails, though with mixed outcomes.² Current schistosomiasis control programmes, however, predominantly rely on praziquantel treatment to allow the effects of MDA to be assessed in the absence of the confounding effects of other interventions. To date, there here have been only two studies investigating the potential long-term effects of MDA on the epidemiology of schistosomiasis, one study using infection data,¹¹ and the other using both infection and immunology data.¹² Here, we extend this work by discussing the potential effects of schistosomiasis MDA on other aspects of both the human and parasite populations.

Effects of anthelmintic treatment on host acquired immunity

Studies in human populations have shown that protective immunity against schistosome infection does develop naturally, albeit over several years.¹³ This slow development of protective acquired immunity has been partly attributed to the undoubted ability of the worms to modulate host immune responses,¹⁴ thereby allowing the parasites to establish chronic infections. Praziquantel alters the schistosome calcium transport channels in the schistosome adult worm tegument, increasing cellular ion permeability, and thus inducing spastic muscular paralysis.¹⁵ This causes morphological changes in the schistosome tegument allowing greater exposure of parasite antigens and thereby driving stronger schistosome-specific antibody and cellular responses.¹⁶ This damage to the tegument allows the host's immune system to attack the worms, leading to their death.¹⁵ Additionally, the clearance of the parasites also removes the cause of immunological down-modulation, increasing the proportion and activation phenotype of antigen presenting cells, CD4+ effector cells, and CD4+ memory T cells.^{17,18} These changes occur in both schistosome-specific and non-schistosome-specific cells and studies investigating mechanisms of action in experimental models of schistosomiasis in mice have shown that the association is causal.¹⁹

The consequences of these two praziquantel-related effects on the intrinsic immune response of the infected host are that the antigen threshold required to mount protective immune responses is achieved²⁰ and the cellular hypo-responsiveness induced by the parasites is reversed.²¹ Furthermore, praziquantel treatment can reverse early pathology in human infections.²² This reversal of early pathology benefits the host in that both re-infection rates and subsequent immunopathology are reduced. Since

resistance to schistosomiasis is only partial, people do still become re-infected, but repeated treatment has been shown to have a greater effect on reducing re-infection rates.²³ Although there is some heterogeneity in the effector responses induced by treatment,²⁴ data from field immuno-epidemiological studies^{16,25} suggest that the immune responses induced by treatment mirror protective immunity that develops naturally, indicating that praziquantel treatment accelerates a process that takes years to occur in untreated individuals.²⁶

Effects of MDA on population-level acquired immunity

The frequency of praziquantel MDA has been prescribed for primary school children, aged 6–14 years, by WHO and ranges from once every 1–2 years to once over the 7 years of primary school for each child, depending on the amount of transmission.²⁷ In countries such as Zimbabwe, ministries of health have embarked on an annual treatment for every schistosome-exposed schoolchild regardless of the level of transmission, so every child will receive up to five treatments—children who miss treatment in 1 year could be treated in the following year, thus ensuring good coverage. However, as has occurred in other countries, MDA programmes run for a specified pre-defined period—for example, Zimbabwe's MDA programme is running for 5 years from 2012 to 2016. Other MDA programmes might not be continued, for various reasons including financial and political willpower.^{9,28} In either case, residual foci of transmission could lead to people in affected areas carrying infections without the benefit of treatment.²⁹ Importantly, it is still not known how long immune responses will persist or decay once the source of antigenic stimulation is removed.

Our prediction is that, in addition to substantially reducing levels of infection, the MDA programmes will initially boost schistosome-specific protective responses in the children aged 6–14 years and this will contribute to a reduction in re-infection rates.¹² This prediction is supported by work on Kenyan car washers²³ and Zimbabwean children³⁰ who showed significant reductions in re-infection rates (accompanied by significant changes in their immune phenotype).

However, it remains unclear for how long this level of acquired resistance will be maintained in the face of reduced natural exposure to infection to boost protective immunity and in the absence of large amounts of antigen released through the killing of worms by praziquantel.¹⁶ The long-term effects of praziquantel treatment on host immune phenotype remain unexplored since there have not been any studies investigating the effects of these changes several years after cessation of MDA. Nonetheless, in the case of schistosome-specific responses and susceptibility to re-infection, we have demonstrated that cessation of MDA after 5 years in areas where there has not been a sustained reduction in overall transmission rate (as might occur in the absence

of additional complementary interventions) can affect the development of schistosome-specific responses.¹² There has already been a precedent in malaria, where following cessation of MDA in Tanzanian children, those who had received malaria chemoprophylaxis had higher rates of pathology (severe malaria) and anaemia compared with non-chemoprophylaxis groups, a difference attributed to the insufficient development of naturally acquired protection in the treated group.³¹ Decay in protective immunity could lead to a rebound in schistosome infection to levels higher than those seen before treatment once drug protection ceases (figure 2). Indeed a rebound in schistosome infection and morbidity after MDA cessation has already been reported from Pemba (Tanzania) and Mali,^{28,32} and this is consistent with predictions from quantitative analyses.¹²

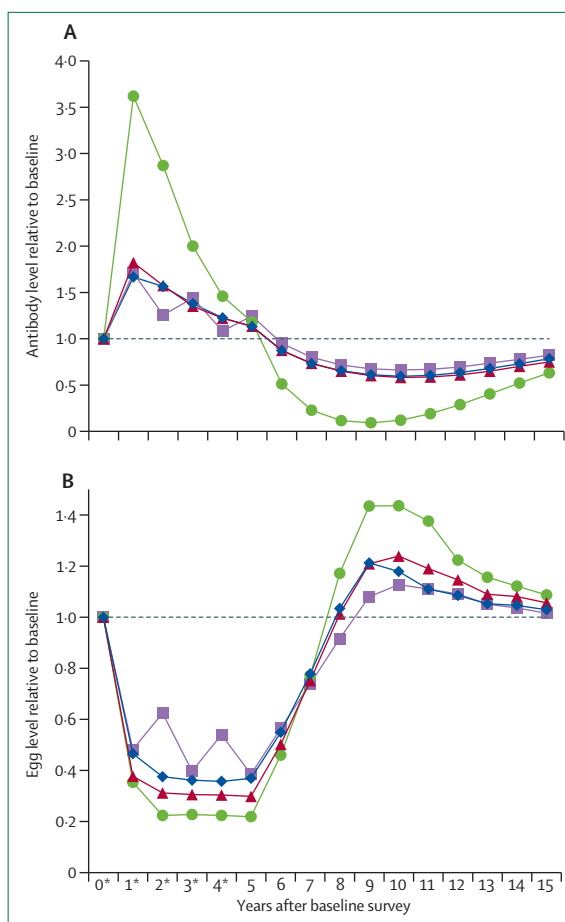


Figure 2: Model-predicted dynamics of protective antibody and egg output during and after MDA for schistosomiasis

Standard treatment applied at yearly intervals for 5 years (asterisks) to a large population of school-aged children (aged 6–15 years) with 75% coverage (blue line). (A) Antibody levels. (B) Egg output. Figures compare results when MDA is given once every 2 years (purple), in a model with 90% coverage (red), and in patients aged 6–34 years (green). This model assumes a short-lived memory response and a worm life span of 6.5 years. Full details are given in Mitchell and colleagues.¹² *MDA was given a day after the survey. MDA=mass drug administrations.

There is also a need to predict the effect of superimposing an anti-schistosome vaccine, when one becomes available, on populations already naturally exposed to the parasite and treated with praziquantel, and thus having some partial protection against infection or re-infection. We have shown¹⁶ that praziquantel treatment enhances immune responses against every WHO schistosome vaccine candidate antigen, including the 28 kDa glutathione S transferase formulated as Bilhvax (figure 3), which has undergone phase 3 clinical trials. Consequently, we have highlighted that the choice of study design and controls in the post-MDA schistosome vaccine trials would need very careful consideration to detect the effects of vaccination above and beyond those of treatment.³³

In mouse experimental models, regulatory responses induced by the helminth parasites as part of their immunomodulatory mechanisms to evade host immune attack reduce the severity or incidence of immune disorders such as colitis and allergic airway inflammation.¹⁹ Human studies^{34,35} have shown that praziquantel treatment increases immune reactivity against allergens and autoantigens. Theoretically, this reactivity gives rise to the potential for praziquantel MDA to exacerbate the clinical manifestations of these immune disorders,¹⁹ generating concerns that MDA programmes could lead to increased levels of these immune disorders in treated populations. However, in practice, these concerns have not been realised. Broadly, the immunological changes in allergic or autoimmune reactivity are quantitative changes that do not translate to clinical disease. Indeed, there are studies^{36,37} documenting that sensitisation to one or more allergens could be highly prevalent without manifesting as a clinically relevant allergy. Similarly, autoreactivity alone does not indicate clinical autoimmune disease. This

finding suggests the existence of complex features of the immune system preventing the translation of immunological changes to clinical pathology in helminth-infected individuals, some of which we have studied in affected human populations.³⁸ For example, the uncoupling of allergic reactivity and clinical disease through higher ratios of total to allergen-specific serum IgE and the epitope specificity of the IgE to stop the clinical expression of allergy symptoms.³⁸ It is also worth factoring in other homeostatic features of the immune system that influence the effect of helminth infections on host health such as the gut microbiome.³⁹ We have recently shown⁴⁰ that in children aged 6 months to 10 years, the gut microbiome abundance and diversity are refractory to praziquantel treatment of *Schistosoma haematobium* infection.⁴⁰ Hence, there is a need to continue monitoring the long-term effects of praziquantel treatment on these responses and clinical disease status in the relevant MDA target populations with the understanding that immunological changes could take months or years to manifest themselves given the complex dynamics of each component in the immune response.

Effects of MDA on parasite environment

Also worthy of consideration is the converse of these immunological changes—ie, the different type of environment for schistosomes that a treated host constitutes and the potential for this new environment to drive selection for different schistosome genotypes or phenotypes. Experimental studies in mice show that schistosome worms display plasticity in their development depending on the host immune phenotype; for example, the development of male worms is dependent on signals from the host immune system.⁴¹ The effects of

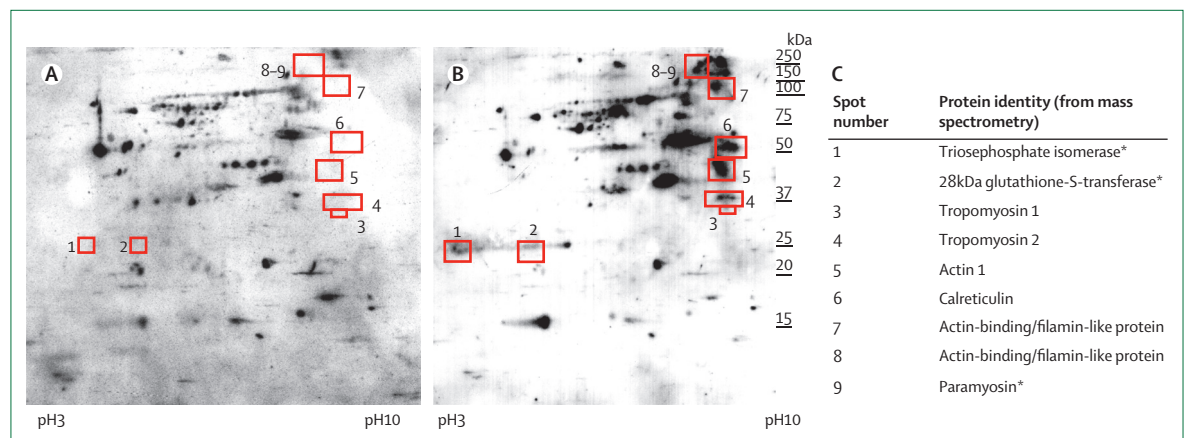


Figure 3: Effects of praziquantel on human schistosome-specific antibody responses: two-dimensional western blot analyses of serological reactivity of the treated cohort comparing pre-treatment with post-treatment responses

The intensity of the IgG1 reactivity against adult schistosome worm antigens in serum pooled from 112 people (male and female) age 5–42 years was compared before and 12 weeks after treatment with the standard dose of praziquantel of 40 mg/kg bodyweight and protein size measured in kilo Daltons (kDa). Adapted from Mutapi and colleagues.¹⁶ (A) Spots (antigens) reacting with serum samples collected at time 0 (before praziquantel treatment). Boxes represent the position where additional spots are present in part B of this figure. (B) Spots reacting with serum samples collected 12 weeks post-treatment. In addition to enhanced recognition of antigens recognised before treatment, additional antigens shown in the numbered boxes were identified. (C) Protein identities of the antigens identified by serum samples after treatment. *Proteins on the current WHO list of schistosome vaccine candidates.

MDA on the developmental plasticity of schistosomes remain to be investigated, particularly to identify whether schistosome transmission and life cycle propagation are altered under MDA pressure as a result of changes in the host immunological environment. Although parasite transmission should be reduced, hypothetically, there could be an overall increase in fecundity or virulence. An experimental study with *Plasmodium chabaudi* found that parasites developing in the face of immunity were more pathogenic when transferred to naive hosts.⁴²

In a meta-analysis⁴³ of 55 reports of trials of praziquantel efficacy, egg reduction rates ranged from 72% to 100% and cure rates ranged from 48% to 100%. Although this heterogeneity arises from several factors, not least pre-treatment infection levels, the effects of differences in host factors cannot be excluded and there is a need to identify whether certain human phenotypes or genotypes will harbour a reservoir of schistosome parasites despite praziquantel treatment. Such human refugia might need supplementary targeting, and immunological or biochemical profiling could help predict individuals in whom treatment failures will occur and these can be targeted by selective population chemotherapy. This targeted treatment might require infection diagnostics more sensitive than parasitological methods, such as antigen-based diagnostics, to ensure identification of people harbouring a reservoir of parasites.⁴⁴

An important variable in human hosts is likely to be pharmacokinetics, which might affect the amount of therapeutic praziquantel available. There is a potential for differing immune responses in children treated with 60 mg/kg praziquantel compared with 40 mg/kg, resulting in lower re-infection rates in children in the group treated with the higher dose.⁵ Praziquantel is metabolised by the cytochrome P450 (CYP) enzyme system in the liver.⁴⁵ Differential expression of these enzymes makes its availability susceptible to variability arising from individual pharmacokinetic heterogeneity, interactions with drugs or substances that induce or inhibit specific isoenzymes of the CYP system taken concomitantly with praziquantel, and liver function (eg, rifampicin used to treat *Mycobacterium tuberculosis* infection can reduce the amount of praziquantel released in the host to below therapeutic levels⁴⁶). To date, no extensive studies have been done to ascertain the relative contribution of these variables in the metabolism and efficacy of praziquantel, and the resultant break-through of parasites despite treatment. Similarly, the level of polymorphism in the isoenzymes of the CYP system⁴⁷ has not been documented in the MDA target populations, nor has there been quantification of the scale of people taking praziquantel concurrently with drugs that affect the bioavailability of praziquantel.

Effects of MDA on parasite population biology

One of the main concerns for any parasite control programme heavily reliant on drug intervention is

possible selection for drug-resistant parasites. The effects of praziquantel MDA on schistosome genetic diversity remain inconclusive.⁴⁸ So far, there have been no validated reports of drug resistance to praziquantel in schistosome worms in human populations, and both field and quantitative studies refute the rapid development of praziquantel resistance.⁴⁹ Nonetheless, heritable variation in praziquantel sensitivity has been shown in schistosome worms experimentally, thus indicating that schistosome worms have the capacity to develop some level of resistance to praziquantel.^{50,51,52} Phylogenetic analyses and indices of schistosome parasite population differentiation have been able to distinguish parasites acquired through re-infection from those that have survived following praziquantel treatment.⁵³ This finding, combined with host genotype characterisation, will be useful for indicating putatively resistant parasites and hosts non-responsive to praziquantel treatment. The advent of schistosome resistance to oxamniquine in the 1970s that halted the *Schistosoma mansoni* MDA programme in Brazil using this drug⁵⁴ indicates a need for complementary interventions for long-term schistosome control programmes.

Consequences of MDA on schistosome population biology include the potential for hybridisation between anthroponotic and zoonotic schistosomes—for example, *S haematobium* worms can hybridise with *Schistosoma intercalatum* or *S mansoni*⁵⁵ as well as with *Schistosoma curassoni* and *Schistosoma bovis*.⁵⁶ The ability of the schistosome species that infect human patients to hybridise with the animal schistosomes provides the potential for extending the host range, and might also affect pathogenicity.⁵⁵ Field studies have already shown that in areas co-endemic for *S mansoni* and *S haematobium*, the efficacy of praziquantel can differ between the species,⁵⁷ and that competition for mates and so-called over-spill can result in hybridisation.⁵⁸ Taking into account the different efficacy of praziquantel in the two main human schistosome species that are co-endemic in some African regions (*S mansoni* and *S haematobium*),

Search strategy and selection criteria

A comprehensive literature search in PubMed using the search terms "Schistosom*" AND ("Mass Drug Administration" OR "MDA*" OR "Preventive Chemotherap*" OR "PCT") AND "praziquantel" AND "human*" returned 96 articles. These articles were exported to Endnote and a title review returned 68 articles, which were read to identify content and relevance. Only three articles had investigated the long-term effect of MDA on host attributes. Two, including one of our own, addressed the effect on re-infection levels, while the third investigated the effect of MDA on HIV transmission. The paucity of studies is partly because the field data required to investigate the effects of MDA are only now becoming available as more countries implement MDA programmes.

hybridisation and its effects on pathology or morbidity require monitoring and further investigation.

To track the effects of MDA on overall host health and parasite population biology and, more crucially, to make predictions that can inform public health interventions and policy, it is essential that host and parasite schistosome epidemiology are closely monitored and related to molecular and genetic characteristics of each. This necessity means following the effects of praziquantel MDA on the typical schistosome epidemiological patterns¹³ and determining whether MDA programmes alter heterogeneity of host immune responses, aggregation of infection, and the age distribution of infection. It is also important to determine the effects of MDA frequency on these patterns in the populations exposed to different schistosome transmission levels.⁵⁹

Conclusion

With the ultimate goal being improvement of both the short-term and long-term health status of at-risk populations, the effects and strategies of schistosome interventions must continually be monitored and assessed in the light of accumulating scientific evidence. Schistosomes have been shown to survive for many years in the host and host responses to schistosome infection develop over similar time scales. As a consequence, population-level shifts in schistosome immunoepidemiology take place slowly, over decades.¹³ Changes in schistosome genetics might occur over even longer time scales. Current evidence indicates that there are substantial health benefits to receiving praziquantel MDA, with very little downside, but it is important that we learn how to sustain these benefits for future generations.

Contributors

FM conceived the idea for this Review. FM, RM, AF, and MW contributed equally to the content of the paper, helped in the preparation of draft manuscript, and reviewed the final version submitted to the journal.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Welcome Wami, Kate Mitchell, Mizuho Fukushima, Takafira Mduluzza, Nicholas Midzi, and the staff of the National Institutes of Health Research Zimbabwe and the Department of Biochemistry at the University of Zimbabwe for their contributions to the work discussed here. The authors thank the Medical Research Council (UK), the Wellcome Trust, The University of Edinburgh ISSF Fund, WHO, and the Thrasher Research Fund for support.

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